Positional Cloning

- The identification of genes based solely on their position in the genome

Targets Suitable for Positional Cloning

- Mendelian traits
- Complex traits
  - Genetically heterogeneous disorders
  - Genes contributing to additive and non-additive genetic variance
- Human traits
- Traits in model organisms

Positional Cloning - Strengths

- Functional information not required
- Broadly applicable
- Aided by Human Genomic Project

Positional Cloning - Weaknesses

- Funtional information absent
- Historically slow and expensive

Positional Cloning - Scale

- 5-9 orders of magnitude reduction required
- Multiple steps
- Multiple technologies

Steps in Positional Cloning

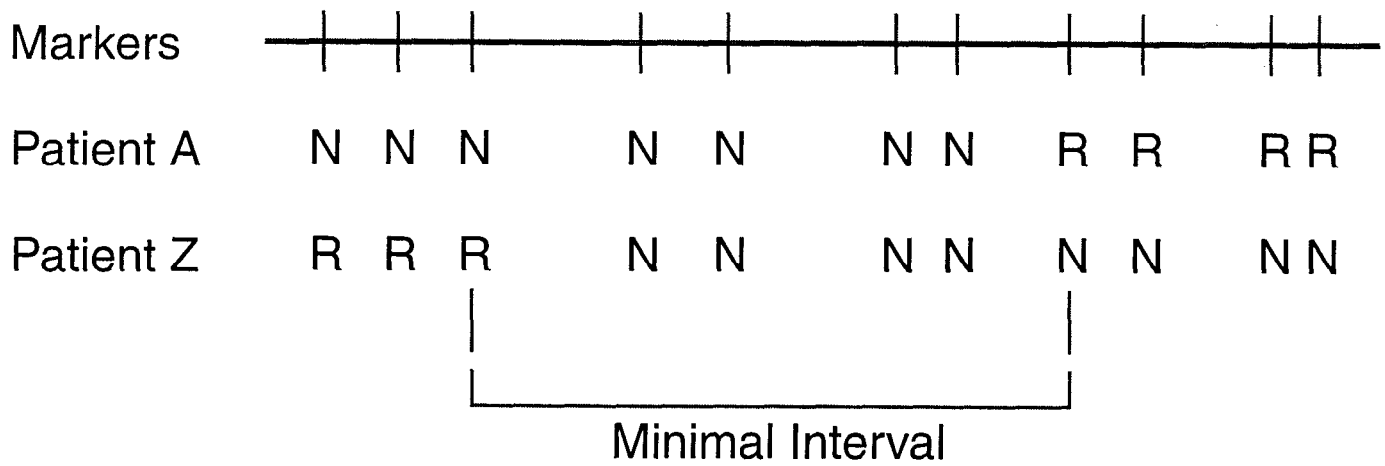
The Complete Path

- Obtain genetic linkage
- Obtain high resolution clone coverage
- Obtain additional markers and genotypes
- Identify minimal critical region
- Identify all genes in critical region
- Evaluate genes for mutations
- Perform association studies to confirm role of gene in disease

Genetic Linkage

- Collect family/patient population
- Genotype at makers spanning the genome
- Analyze and quantitate support

Identification of Minimal Critical Interval



Shortcuts in Positional Cloning

- Use of isolated populations and founder effects
- Positional candidates
- Triplet nucleotide repeat expansions
- Cytogenetic abnormalities

Isolated Populations

Geographic Isolation

- Tristan de Cunha
- Finland
- Iceland
- Japan
- Sardinia

Isolated Populations

Religious Isolation

- Jews
- Amish
- Hutterites

Isolated Populations

Cultural Isolation

- Tribal populations
  - Bedouins
  - Berbers
  - Navajo
- Gypsies
- Cajuns

Non-Mendelian Traits

Linkage Limitations

- Variation in gene not necessary and sufficient for disease
- Development of nonparametric methods

Non-Mendelian Traits

Rare Mendelian Forms

- Alzheimer's Disease
- Type II Diabetes - MODY

Non-Mendelian Traits

Concept of Lambda

- Relative risk conferred by the gene in question

$$\lambda = \frac{\text{Risk to a family member}}{\text{Risk to the general population}}$$

Range of λ_s Values

- Huntington Disease=4000
- Cystic Fibrosis=900

- Autism=75
- Schizophrenia=10
- Alzheimer's Disease, Prostate Cancer=5

Non-Mendelian Traits

Approximate Required Sample Sizes

λs	Affected Sibling Pairs
3.0	100
2.0	200
1.5	400

Future of Positional Cloning

- Identity of all genes will be known
  - UniGene clusters
  - Full-length cDNA databases
  - Genomic DNA sequence

Future of Positional Cloning

- Location of all genes will be known

Future of Positional Cloning

- Bi-allelic polymorphisms
  - High density
  - Non-gel assays
  - High through-put automation

Future of Positional Cloning

- Polymorphisms in genes
- Large-scale association studies

Future of Positional Cloning

Needed Now

- Phenotype definition
- Family/patient collection